Melatonin in doctors and nurses working nightshifts

MIDNIGHT (Melatonin **I**n **D**octors and nurses working **NIGHT**shifts) **TRIAL**

This protocol has regard for the HRA guidance and order of content

RESEARCH REFERENCE NUMBERS

EudraCT number	2015-004106-42
REC number	16/NS/0010
NHS R&D number	2016/AN001
ISRCTN number	ISRCTN15529655

TRIAL REGISTRY NUMBER AND DATE

PROTOCOL VERSION NUMBER AND DATE	Version 4.0 16/06/2016 3-047-15

OTHER RESEARCH REFERENCE NUMBERS

SPONSOR / CO-SPONSORS / JOINT-SPONSORS	University of Aberdeen / NHS Grampian
FUNDER	BJA / RCoA
Funder reference number	N/A

SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, GCP guidelines, the Sponsor's SOPs, and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the study publically available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

Chief Investigator:

Signature:

Date:
16/06/2016

Name: (please print):

Helen Frances Galley

Statistician:

Signature:

Date:
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KEY TRIAL CONTACTS

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Joint-sponsor(s)/co-sponsor(s)	University of Aberdeen and NHS Grampian
Funder(s)	British Journal of Anaesthesia/Royal College of Anaesthetists
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TRIAL SUMMARY

Trial Title	Melatonin in doctors and nurses working nightshifts	
Internal ref. no. (or short title)	MIDNIGHT Trial	
Clinical Phase	Phase 2	
Trial Design	Randomised, double blind, placebo controlled, cross over	
Trial Participants	Intensive care unit medical and nursing staff	
Planned Sample Size	32	
Treatment duration	3 nights x 2 occasions	
Follow up duration	End of final study visit	
Planned Trial Period	3 years	
	Objectives	Outcome Measures
Primary	To determine the feasibility of a trial of Circadin vs placebo in medical and nursing staff working nightshifts on the intensive care unit.	Recruitment and randomisation of 25 individuals completing both arms of the crossover design.
Secondary	Determine effect of night shift working on transcriptome. Determine effect of Circadin on transcriptome. Determine effect of night shift working on cytokine profile. Determine effect of Circadin on cytokine profile Determine metabolism of Circadin Determine effect of Circadin on sleep measures	Differential gene expression between baseline and end of shift on Day 1, and end of shifts series on Day 4 . Differential gene expression between placebo and active arms on Day 4. Serum IL-6 and TNFα levels at baseline, end of shift on Day 1 and on Day 4. Serum IL-6 and TNFα levels after placebo and active arms on Day 4. Serum melatonin and 6-hydroxymelatonin sulphate levels at each time point Verran and Snyder-Halpern sleep scale, Epworth sleepiness scale, data from wristband activity monitor

	Determine effect of Circadin on psychomotor function Determine whether usual sleep habits impact on effect of Circadin Participants' views about the trial.	Psychomotor vigilance task, double digit addition test. Usual sleep habits and owl-lark questionnaires. Post trial questionnaire and focus group.
Intervention	Circadin™ or matching placebo	
Formulation, Dose, Route of Administration	Oral, 6mg, modified release tablets	

FUNDING AND SUPPORT IN KIND

FUNDER(S) (Names and contact details of ALL organisations providing funding and/or support in kind for this trial)	**FINANCIAL AND NON FINANCIAL SUPPORT GIVEN**
British Journal of Anaesthesia/Royal College of Anaesthetists	Financial support for the study.
Flynn Pharma	Provision of Circadin and matching placebo, free of charge.

ROLE OF STUDY SPONSOR AND FUNDER

The trial is co-sponsored by the University of Aberdeen and NHS Grampian. It is funded by a grant award from the British Journal of Anaesthesia / Royal College of Anaesthetists through the National Institute of Academic Anaesthesia. Neither the sponsor nor the funder has had a role in trial design and will have no role in data analysis, interpretation, manuscript writing, and dissemination of results. Neither the sponsor nor the funder will control the final decision regarding any of these aspects of the trial.

ROLES AND RESPONSIBILITIES OF TRIAL MANAGEMENT COMMITEES/GROUPS & INDIVIDUALS

Trial management group

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Trial steering committee

The draft charter/terms of reference and composition are given in Appendix 1.

Data and safety monitoring committee

The draft charter/terms of reference and composition are given in Appendix 2.

Protocol contributors

The contributors to this protocol are Professor Helen Galley, Professor Nigel Webster and Dr Lorna Aucott.

Key words; melatonin; sleep; nightshift; intensive care unit; medical staff

LIST of CONTENTS

LIST OF ABBREVIATIONS

AE	Adverse Event
APR	Annual Progress Report
AR	Adverse Reaction
CA	Competent Authority
CI	Chief Investigator
CRF	Case Report Form
CRO	Contract Research Organisation
CSM	Composite Scale of Morningness
CTA	Clinical Trial Authorisation
CTIMP	Clinical Trial of Investigational Medicinal Product
DMC	Data Monitoring Committee
DSUR	Development Safety Update Report
EC	European Commission
EMEA	European Medicines Agency
ESS	Epworth Sleepiness Scale
EU	European Union
EUCTD	European Clinical Trials Directive
EudraCT	European Clinical Trials Database
EudraVIGILANCE	European database for Pharmacovigilance
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use.
IL	Interleukin
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trials Number
MA	Marketing Authorisation
MHRA	Medicines and Healthcare products Regulatory Agency
MS	Member State
NHS R&D	National Health Service Research & Development

PC-PVT	Psychomotor Vigilance Test
PI	Principal Investigator
PIS	Participant Information Sheet
QA	Quality Assurance
QC	Quality Control
RCT	Randomised Control Trial
REC	Research Ethics Committee
REM	Rapid Eye Movement
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDV	Source Data Verification
SOP	Standard Operating Procedure
SmPC	Summary of Product Characteristics
SSI	Site Specific Information
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMG	Trial Management Group
TNF	Tumour Necrosis Factor
TSC	Trial Steering Committee
TMF	Trial Master File
VSH	Verran and Snyder-Halpern (Sleep Scale)

STUDY PROTOCOL

Melatonin in doctors and nurses working nightshifts- MIDNIGHT Trial

1 BACKGROUND

Circadian rhythm is controlled by cells located in the suprachiasmatic nucleus (SCN) which receive information about the level of illumination from the eyes and feed this information to the pineal gland which secretes the hormone melatonin. During daytime, circulating melatonin concentrations are very low. The start of melatonin secretion, 'dim light melatonin onset' (DLMO) is ~2h before sleep onset, peaking around 4am, and coinciding with low body temperature and alertness [1]. In night shift workers, until the DLMO has altered and sleeping is 'in phase' with melatonin secretion, workers try to sleep during maximum times of alertness and performance [2,3]. Adaptation to night shifts usually takes around 1 day for each hour of change, but some night shift workers never adapt [4]. An ICU presents a highly demanding workplace and failure to cope with adaptation to irregular night working may impact on patient safety [5]. A very recent study reported sleepiness and fatigue during night shifts in ICU nurses, coupled with increased response times and decreased mathematical problem solving productivity [6].

Around 10% of genes are controlled by circadian rhythm and there are gene transcript changes in the blood of human volunteers after sleep deprivation [7] or when sleep is out of phase with melatonin secretion [8]. Shift work involving circadian disruption is associated with increased risk of cancer [9,10] and other adverse health outcomes such as mental health issues [11], cardiovascular disease [12,13] and reproductive problems [14] have been reported. It has been suggested that melatonin may promote beneficial pathways [15-17]. Although studies of changes in immune function in shift workers are less clear [18] it is well known that sleep deprivation results in changes in cytokines particularly interleukin-1 (IL-1) and tumour necrosis factor (TNF)α [19-23]. Melatonin affects genes, epigenetic processes and transcriptional activators which regulate cytokine responses and this may modulate the changes induced by sleep deprivation [21,24,25].

Poorer cognitive performance has been reported during night shifts compared to day shifts [26,27]. Exogenous melatonin was 'remarkably effective' in preventing or reducing 'jet lag' [26] but effects on sleep were less clear [29,30]. In night shift workers, melatonin was beneficial in some studies [31-33]. The effect of exogenous melatonin on either cognitive function or the human transcriptome has not been reported in night shift workers. ICU nurses were recently reported to improve their ability to adapt to night shifts in part by napping during night shifts, which is concerning [6].

At Aberdeen Royal Infirmary, trainee doctors work 4 consecutive nights at approximately 6 week intervals and nurses work 7 consecutive nights at 4 week intervals. We hypothesise that exogenous melatonin may be beneficial at a molecular/physiological level. The aim of this study is to investigate the effects of exogenous melatonin compared to placebo in medical and nursing staff working night shifts. We will assess affects on sleeping patterns, psychomotor vigilance and biochemical measures and effects on the transcriptome will be determined. We will assess, in a double blinded randomised controlled cross-over pilot study, whether nightly doses of oral melatonin are able to improve sleep and psychomotor vigilance and modify gene transcripts and cytokines.

2 RATIONALE

Poorer cognitive performance and increased time to undertake tasks have been reported in people working night shifts, compared to day shifts. Adaptation to night shifts requires sleeping patterns and endogenous melatonin secretion to be 'in phase'. Melatonin has effects

on genes, and changes to the human transcriptome in healthy subjects when their sleep pattern is out of phase with melatonin secretion has been reported. There are no reports of the effects of exogenous melatonin on transcripts in night shift workers. The aim of this pilot study is to determine the effects of exogenous melatonin administration compared with placebo in medical and nursing staff working night shifts. This pragmatic pilot study will assess, in a double blinded randomised cross-over trial, whether melatonin given before sleep time can improve sleep and psychomotor vigilance and modulate transcript changes. In the placebo phase we will be able to determine if the transcriptome changes described when sleep is out of phase with melatonin secretion are also seen in actual night shift workers. Changes in gene transcripts may explain the health disadvantages of shift working and melatonin may be a useful intervention.

2.1 Assessment and management of risk

There is no evidence of risk of melatonin administration even at very high doses from very many studies in both healthy people and disease conditions. The potential benefit to the individual participant is limited to the possibility of improved sleep cycle during one of the night shifts.

This trial is categorised by the MHRA as **not** being a Clinical Trial of an Investigational Medical Product (CTIMP).

The study represents use of a licensed product with an established safety profile in a subject population outside of that licence and indication but not for a clinical condition. The safety and efficacy of melatonin has been studied in populations of similar age to those we are studying (>18 years) and in paediatric populations (to manage sleep disturbance in children with neurodevelopmental disorders).

3 OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS

The aim of this pilot study is to investigate the feasibility of this trial design to assess the effects of exogenous melatonin (Circadin) compared to placebo in medical and nursing staff working night shifts and the most appropriate endpoint measures for future studies. This is a pilot study- there are no previous data on which to base a sample size calculation. We will explore effects of Circadin on sleeping patterns, psychomotor vigilance and biochemical measures and on the transcriptome. The various measures of sleep will include quality, latency, disturbance, and sleepiness. Psychomotor function will be assessed using reaction time testing and double digit addition tasks. Cytokine profiles, melatonin and 6-hydroxymelatonin concentrations and gene transcripts will be measured. Since much of previous data have not been reported in people actually working night shifts, this study will generate important data even in the absence of any effect of Circadin, which is unlikely.

3.1 Primary objective

The primary objective is to undertake a pilot feasibility trial of 6mg slow release melatonin (Circadin^{TM}) before sleep periods compared to placebo in medical and nursing staff working night shifts at Aberdeen Royal Infirmary. The study is a pilot study with no formal sample size calculation.

3.2 Secondary objectives

The secondary objectives are to:

- Determine effect of night shift working on the transcriptome.
- Determine effect of Circadin on the transcriptome.
- Determine effect of night shift working on the cytokine profile.
- Determine effect of Circadin on the cytokine profile.

- Determine metabolism of Circadin.
- Determine effect of Circadin on sleep measures.
- Determine effect of Circadin on psychomotor function.
- Determine whether usual sleep habits impact effect of Circadin
- Determine participants' views about the trial.

3.3 Primary endpoint/outcome

The primary endpoint is successful completion of the trial, defined as recruitment, randomisation and protocol completion of 25 individuals ie both arms of the crossover design. We aim to recruit 32 subjects to account for dropout and non-completion.

3.5 Secondary endpoints/outcomes

Objectives	**Outcome Measures**	**Timepoint(s) of evaluation of this outcome measure (if applicable)**
Primary Objective	Randomisation of 32 subjects with the aim of 25 completing both arms of the crossover design. This will allow for at least 20% attrition rate which is fairly standard in such studies.	
Secondary Objectives	Determination of drop out, non completion and retention rate	Trial end.
	Differential gene expression	Blood samples on Day 1 before shift, and end of shifts series on Day 4.
	Differential gene expression between placebo and active arms.	Blood samples Day 4 after each shift series.
	Serum IL-6 and TNFα levels.	Blood samples on Day 1, and end of shifts series on Day 4 .
	Serum IL-6 and TNFα levels after placebo and active arms.	Blood samples Day 4 after each shift series.
	Serum melatonin and 6-hydroxymelatonin sulphate levels at each time point	Blood samples on Day 1 before shift, and end of each shift for shift series.
	Verran and Snyder-Halpern sleep scale, Epworth sleepiness scale, data from wristband activity monitor.	VSH before each shift. ESS before, during and after each shift. Activity monitoring during each sleep period.
	Psychomotor vigilance task, double digit addition test	PVT and DDAT before and after each shift
	Usual sleep habits and owl-lark questionnaires.	Before randomisation.
	Questionnaire about trial.	Trial end.
	Focus group on trial.	Trial end (requires additional consent)

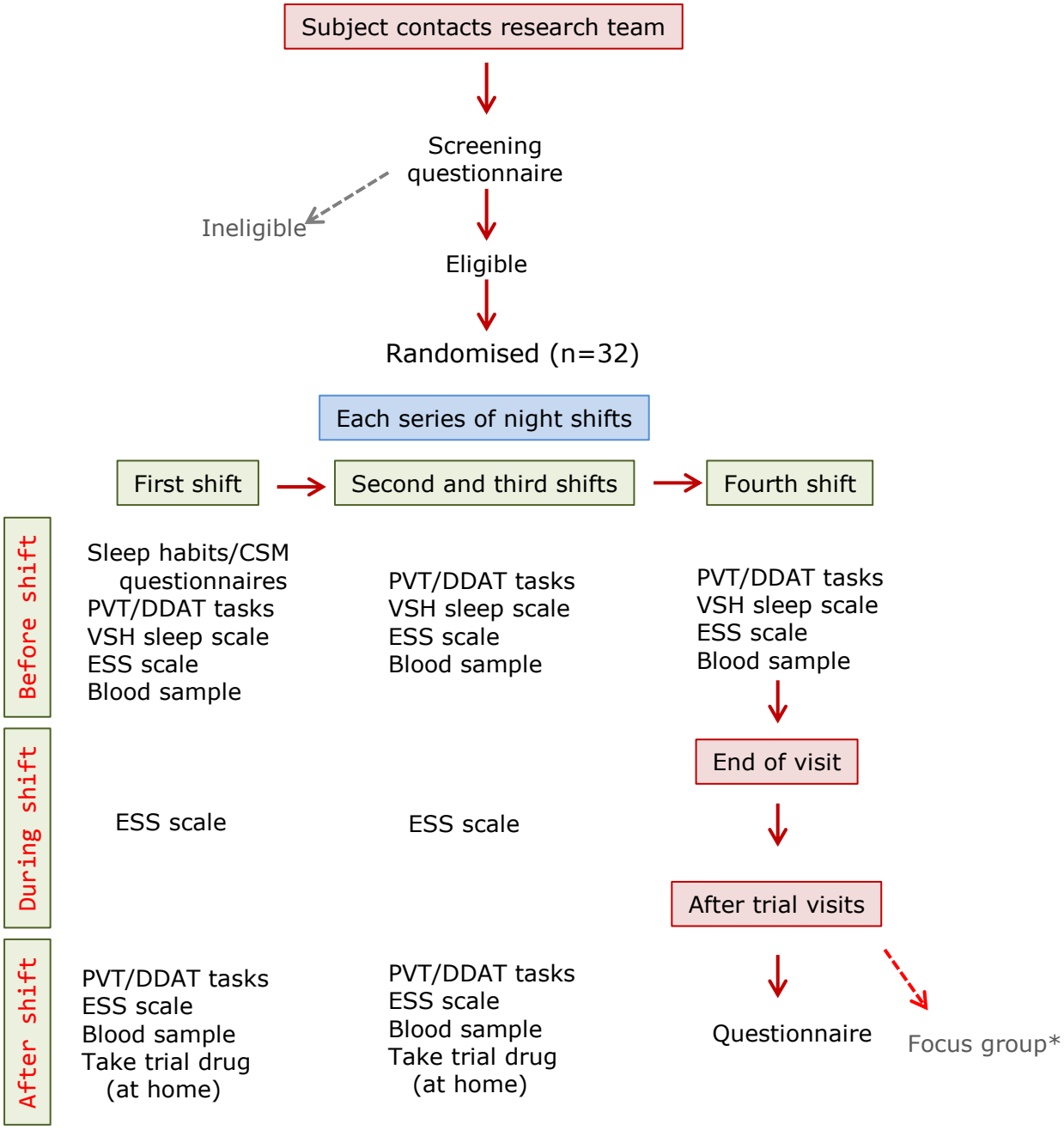

Figure 1

Summary of the trial design.

4 TRIAL DESIGN

This is a randomised, double blind, placebo controlled crossover pilot study. See Figure 1 and Table 1.

5 STUDY SETTING

This is a single centre study and will recruit staff working within Aberdeen Royal Infirmary, NHS Grampian. Doctors and nurses who routinely undertake periods of night shift working will be recruited by advertisement and global emails from a third party. Some parts of the study will be completed within the volunteers' home setting – eg questionnaire completion.

6 ELIGIBILITY CRITERIA

Following written informed consent, 32 participants of either sex, non-smokers, not taking regular medicine and with no health complaints will be eligible. Exclusion criteria will be pregnancy, breastfeeding, *ad hoc* use of sedatives, and known allergy to drug contents. Anyone with pre-existing health problems will not be recruited. A simple screening questionnaire will be used prior to recruitment (Appendix 4).

6.1 Inclusion criteria

Any male or female member of staff working nightshifts to a regular pattern and who can commit to both arms of the study ie 2 series of night shifts approximately 4-6 weeks apart, will be eligible.

6.2 Exclusion criteria

We will only recruit subjects who do not have a body mass index within the obese or overtly underweight range and who do not have self reported sleeping issues before the study starts. Other exclusion criteria include pregnancy (or trying to get pregnant- female participants), breast feeding, current use of sedatives, hypnotics, anti-histamines and herbal sleep remedies and known allergy to drug contents. Female subjects will be asked to confirm that they are not trying to get pregnant and that they one of the following apply: using adequate contraception and will continue to do so for the duration of the trial, or that they have been sterilised, or they are post-menopausal, not sexually active, or infertile (see Appendix 4).

7 TRIAL PROCEDURES

The study design is summarised in Figure 1 and the timing of tasks, questionnaires and samples are shown in Table 1. The burden of tasks and questionnaires have been considered with regards to burden and fatigue.

7.1 Recruitment

The study will be advertised to volunteers by global emails and posters. Volunteers will make themselves known to any of the trial investigators. They will then be given a copy of the participant information sheet and if they wish to take part after the study is explained to them they will be asked to sign a consent form. Consent can be obtained from any delegated member of the research team who has undergone GCP and taking consent training.

7.1.1 Screening

Before the study, subjects will provide basic demographic information (Appendix 4). Anyone who has a chronic health issue, or fulfils any of the other exclusion criteria will not be recruited.

7.2 Consent

The Chief Investigator (CI) retains overall responsibility for the informed consent of participants but a delegated member of the research team will also be able to take informed consent. The right of a participant to refuse participation without giving reasons will be respected and participants remain free to withdraw at any time from the trial without being

obliged to give reasons. However we will record a reason if offered one since this is valuable information for a feasibility study such as this. Once recruited, each subject will be assigned a unique ID number and any identifiable information will be kept securely in a locked office to which only the chief investigator has access.

7.2.1 Additional consent provision for collection and use of participant data and biological specimens in ancillary studies

Any biological samples remaining will be stored in a biobank, pending use in further related research, subject to any ethical requirements. Samples will be anonymised with a unique identification number. Participants will be asked to consent to such storage; those who choose not to consent to this will still be eligible to take part but their samples will not be placed into the biobank. We will also request consent from subjects to be contacted after the trial is complete to ask about taking part in a focus group to find out participants' views about the trial.

7.3 Randomisation scheme

Volunteers will be randomized to receive either placebo or melatonin and will then receive the opposite during the next study intervention. As such they will be acting as their own controls. Randomisation will be by random number provided by a third party not involved in the trial, in blocks of 8 such that for each 8 subjects randomised, four will receive melatonin first and 4 will receive placebo first. This block allocation will ensure that within a close time window (within 4-6 weeks) to minimise seasonal effects. The schedule will be provided to the Clinical Trials Pharmacy in advance.

7.3.1 Method of implementing the allocation sequence

Study drug or an identical placebo will be dispensed from pharmacy by the research pharmacist according to a previously supplied randomisation code list. This will be prepared by an independent statistician.

7.4 Blinding

Researchers and volunteers will be blinded at all times to the treatment allocation. Placebo and melatonin will be tablets of identical appearance. Blinding will be maintained unless it is considered necessary to unblind for safety reasons. This can be rapidly achieved by contacting Pharmacy.

7.5 Unblinding

The code breaks for the trial will be held in the clinical trials pharmacy. In the event that unblinding is required then a formal request for unblinding will be made by the CI. Should unblinding be required then the information will be disseminated to the Data Monitoring Committee (DMC) for review in accordance with the DMC Charter.

7.6 Baseline data

Questionnaires to record usual sleeping habits will be completed. We will use the usual sleep habits questionnaire (Appendix 5), the Composite Scale of Morningness (CSM), also known as the owl and larks questionnaire (Appendix 6) [37-41], and the Verran and Snyder-Halpern (VSH) sleep scale (Appendix 7) [34,42,43] to provide some baseline information. CSM scores have been found to correlate with self-reported alertness, rising times and retiring times across various cultures. This will be done once before the first night shift and will relate to usual habits when not working night shifts.

7.7 Trial assessments

Immediately before the first shift subjects will have a baseline blood sample taken and will complete the Epworth Sleepiness Scale (ESS) and the VSH sleep scale [34,42,43]. A baseline personal computer based psychomotor vigilance task (PC-PVT) will be undertaken [44,45]. A double digit addition test (DDAT) will also be used to test problem solving performance, where subjects have to repeatedly add two random double-digit numbers together for a period of 5 minutes (example given in Appendix 8). The percentage of correct answers and the time taken to undertake each addition, plus any lapses, defined as a response time of more than 10s, will be recorded. The worksheet for this is created online and a different sheet will be used each time: http://www.math-aids.com/Addition/Addition_Drills.html.

The ESS will be repeated mid-way through the shift. At the end of the shift, subjects will have another blood sample taken and undertake the PC-PVT and the ESS again before going home, where they will take 6mg melatonin (as Circadin) or a matching placebo with a small snack before going to bed. The means and duration of travel home and the time of dosing and bedtime will be recorded. Subjects will wear a wristwatch style activity monitor during the sleep period, which records activity, sleep and restlessness, REM sleep duration, body temperature and heart rate data that can be downloaded for subsequent analysis.

Subjects will be asked to wear sunglasses on their journey home if it is light. Subjects will be asked not to attempt to sleep during the day before starting the first night shift and to go to bed as soon as possible when they get home after the shift has ended. They will be asked not to nap during the shift. They will also be asked to refrain from consuming acohol whilst study visits are ongoing. The VSH sleep scale and ESS will be completed again at home when they wake. All PC-PVT tests will be undertaken with a researcher present; the mid-shift ESS will be completed by the subject but a text message reminder will be sent to aid compliance. On each of the next 2 subsequent shifts subjects will undertake the same processes. Around 4-6 weeks later when subjects work another series of night shifts, they will go through the same procedure, but take melatonin if they previously took placebo, and vice versa. Consideration has been given the number of tasks and questionnaires at any one time point to minimise burden and inconvenience such that the time requirement will be no more than 15 minutes in total at any time point.

Biochemical assays

Serum melatonin will be measured using liquid chromatography-tandem mass spectrometry, a method which we have developed in-house. The major metabolite of melatonin, 6-hydroxymelatonin, will be measured in serum as the sulphated form in serum using enzyme immunoassay. Biochemical tests will include urea and electrolytes, liver function tests and differential leucocyte counts. Cytokines (IL-1/6 and TNFα) will be measured using high sensitivity immunoassays. Changes in melatonin/6-hydroxymelatonin and cytokines between melatonin and placebo and between shifts will be determined.

Psychomotor vigilance testing and addition testing

The PC-PVT requires sustained attention and measures how subjects respond to a visual stimulus- a light comes on randomly every few seconds for 5–10 minutes and subjects click as soon as the light appears. In addition to reaction time we will also record when the mouse is not clicked when the light comes on, thus counting the number of lapses in attention of the subject. The PVT does not allow learning and is unaffected by individual aptitude. The software is freely available to download and incorporates data analysis capability. A two digit addition test will also be used to test problem solving performance, where subjects have to repeatedly add two random double-digit numbers together for a period of 5 minutes. The percentage of correct answers and the time taken to undertake each addition, plus any lapses, defined as a response time of more than 10s, will be recorded.

Sleep scales/questionnaires

The VSH sleep scale is a validated scale which uses 100mm visual analogue scales to record sleep disturbance, efficiency and supplementation. This will be used to assess how subjects slept the night before the study, then after each night shift to compare quantitative data between placebo and melatonin and between shifts. The ESS which assesses 'sleepiness' and the CMS questionnaires will provide semi-quantitative/descriptive information.

Wristband activity/sleep monitor

These unobtrusive devices were designed for activity or fitness monitoring but can also be used to record periods of sleep, including REM sleep (via movement, heart rate and body temperature), and any restlessness. Subjects will be asked to wear one of these during the sleeping period after each shift. Data can then be downloaded to an online application for analysis. There are several models available with effective sleep analysis capability.

Transcriptome analysis

Blood samples will be taken from all subjects for transcriptome analysis during each series of shifts as follows: 1. Before the first shift (baseline, 'in phase'). 2. Before the second shift (completely 'out of phase'). 3. Before the fourth shift ('beginning to readjust'). Total RNA will be isolated from all samples using the Paxgene system which produces samples which are stable for many months.

7.8 Long term follow-up assessments

There will be no long term follow-up assessments.

7.9 Withdrawal procedures

Should participants wish to withdraw during the actual study visit the trial process will depend on what stage of the study is reached. If the drug has not yet been administered, then the participant can withdraw immediately and replaced with another eligible candidate. If melatonin or placebo has been given then no further drug will be given and no more samples will be obtained. Data and samples obtained with consent will be retained. If the participant withdraws the reasons, if given, will be recorded. If the target of 25 completers (ie both arms) is not reached after 32 randomised subjects we will continue to recruit if time allows.

7.10 Storage and analysis of samples

Blood samples (20ml) will be obtained by venepuncture by a appropriately trained person. Samples will be placed into appropriate blood collection tubes. Samples will be transported within 2h under containment level 2 rules (SOP-IMS-006) in the Institute of Medical Sciences (IMS) for preparation of serum or RNA and storage according to a standard operating procedure (SOP-IMS-005). Samples will be labelled with a unique anonymised ID number only. Serum and RNA samples will be stored immediately at -70 (+/- 10) degrees C in a designated ultra low temperature freezer with daily temperature monitoring (SOP-IMS-001). All samples will be analysed locally.

We recognise that it is the responsibility of the trial site to ensure that samples are appropriately labelled in accordance with the trial procedures to comply with the 1998 Data Protection Act. Biological samples collected from participants as part of this trial will be transported, stored, accessed and processed in accordance with national legislation relating to the use and storage of human tissue for research purposes and such activities shall at least meet the requirements as set out in the 2004 Human Tissue Act and the 2006 Human Tissue (Scotland) Act.

7.12 End of trial

The end of the trial is defined as 6 months after the last volunteer has received both study treatment arms – this is to allow final sample handling and data analysis and conduct and analysis of focus groups.

8 TRIAL MEDICATION

Melatonin will be administered as Circadin (6mg as 2mg tablets, Flynn Pharmaceuticals Ltd.) which has EMA regulatory approval and is a slow release formulation with a blood concentration profile resembling that of endogenous melatonin. Placebo tablets will also be manufactured for us by Flynn. Both the melatonin and placebo will be provided free of charge and will be dispensed by the Clinical Trials Pharmacy who will also be responsible for drug accountability. Commercial stocks of Circadin will be delivered, with a self-life of 2.5-3 years under normal pharmacy conditions. The bulk placebo will have nominally a 3 year shelf-life and the bulk product will be stored in pharmacy in conditions to protect it from light, moisture and excessive temperature. HDPE bottles will be used for post-randomisation dispensing of both active drug and placebo. Drug accountability will be delegated to the Clinical Trials Pharmacist, Patricia Cooper.

8.1 Name and description of the interventional product

The product is Melatonin (Circadin™) and an identical placebo tablet both provided by Flynn Pharma Ltd.

8.2 Legal status of the drug

Melatonin is currently licenced for use in the UK but the study has been classified by the MHRA as **not** being a CTIMP and therefore does **not** require a Clinical Trial Authorisation (CTA). The drug will however only to be used by the named investigators, for the volunteers specified in this protocol, and within this trial only.

8.3 Summary of Product Characteristics (SmPC)

Please see the Investigator Brochure (IB) and the Summary of Product Characteristics (SmPC), available at https://www.medicines.org.uk/emc/medicine/25643.

Flynn Pharma has committed to inform the Chief Investigator should there be any updates to the SmPC.

8.4 Drug storage and supply

Drug (active and placebo) storage will be at <25°C. See SmPC for details. The shelf life is 3 years.

Melatonin and identical placebo tablets have been supplied by the manufacturer (Flynn Pharmaceuticals Ltd) and will be stored in the Aberdeen Royal Infirmary Clinical Trials Pharmacy. A prescription sheet will be sent to pharmacy indicating the trial number, unique identifier and subject name. Pharmacy will dispense active or placebo drug depending on a randomisation list previously provided. Labelling will be according to Annex 13 of Volume 4 of The Rule Governing Medicinal Products in the EU: Good Manufacturing Practices".

Empty bottles and unused medication will be returned to Pharmacy who will maintain drug accountability records.

8.5 Preparation and labelling

Flynn Pharma have supplied the Circadin and matching placebo tablets (2mg) as a single bulk supply from a single batch for dispensing by the Clinical Trials Pharmacy. Commercial stocks of Circadin are provided. Both active and placebo drug will have a shelf-life of 3 years. Drug accountability will be delegated to the Clinical Trials Pharmacist, Patricia Cooper.

Table 1 **Study Overview (**applies to both shift series)

Shift	Blood sample	Sleep habits/CSM questionnaire	PVT/DDAT	Trial drug	VSH sleep scale	ESS	Post trial questionnaire	Focus group*
First shift before shift during shift end of shift before sleeping	✓✓✓ ✓	✓	✓ ✓	 ✓	✓	✓ ✓ ✓		
Second shift before shift during shift end of shift before sleeping	✓		✓ ✓	 ✓	✓	✓ ✓ ✓		
Third shift before shift during shift end of shift before sleeping	✓		✓ ✓	 ✓	✓	✓ ✓ ✓		
Fourth shift before shift	✓✓✓		✓		✓	✓		
After all visits							✓	✓

✓ = Blood sample for gene array ✓ = Blood sample for melatonin/cytokines ✓ = Blood sample for pathology CSM = composite scale of morningness PVT/DDAT= psychomotor vigilance task/double digit addition test VSH = Verran and Snyder-Halpern sleep scale ESS = Epworth sleepiness scale * requires additional consent

8.6 Dosage schedules

Subjects will receive an oral dose of 6mg Circadin or a placebo of identical appearance (as 3 x 2mg tablets) just before bedtime, on three consecutive nights, on two occasions. One of those occasions the subjects will receive the active Circadin and on the other they will receive the placebo. The order will be randomised. Subjects will be asked to take the medication 1-2 hr before planned bedtime/sleeping time with a small snack. The time of dosing, the time of bedtime and the type of snack will be recorded.

8.7 Dosage modifications

There will be no dosage modifications allowed.

8.8 Known drug reactions and interaction with other therapies

Treatment will be stopped if a patient develops an unexpected reaction thought to be due to Circadin administration. This might include, but is not limited to, vomiting, diarrhoea or suspected anaphylaxis. Fluvoxamine or nifedipine interfere with the metabolism of melatonin but are not considered to be harmful. Subjects taking these drugs would not be eligible for the study and participants would be withdrawn should they require these drugs for medical reasons during the study.

8.9 Concomitant medication

Participants receiving chronic medication other than oral contraceptives will not be recruited. If subjects require medication during the trial this will be allowed, apart from fluvoxamine, nifedipine, sedatives or other drugs likely to cause drowsiness, but will be recorded.

8.10 Trial restrictions

Apart from specified medications, avoidance of sunlight during the return home after the night shifts and not consuming alcohol there are no trial restrictions.

8.11 Assessment of compliance

Subjects will be take their trial drug at home and asked to return the empty container. They will be asked to confirm the time that they took the trial drug. Non-compliance will be recorded.

9 PHARMACOVIGILANCE

9.1 Definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.
Adverse Reaction (AR)	An untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant. The phrase "response to an investigational medicinal product" means that a causal relationship between a trial medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • results in death • is life-threatening • requires inpatient hospitalisation or prolongation of existing hospitalisation • results in persistent or significant disability/incapacity • consists of a congenital anomaly or birth defect Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences. NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the trial treatments, based on the information provided.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product in question set out: • in the case of a product with a marketing authorisation, in the summary of product characteristics (SmPC) for that product • in the case of any other investigational medicinal product, in the investigator's brochure (IB) relating to the trial in question

9.2 Operational definitions for (S)AEs

Investigators who are clinically qualified at consultant level will be responsible for the detection and documentation of events meeting the criteria and definitions detailed above. For this trial this will be Professor Nigel Webster.

The Chief Investigator and the clinical team will make decisions as to whether any such events are unexpected in terms of timing or severity and considered related to the study drug, with advice from the DMC as necessary.

All AEs and SAEs will be recorded from the time of study entry until the end of the last study visit.

Depending on severity, when an AE/SAE occurs, the Investigator will review any documentation (e.g. hospital notes, laboratory and diagnostic reports) related to the event and record all relevant information in the CRF and on the AE or SAE form.

Information to be collected will include dose of any medication, type of event, onset date, Investigator assessment of severity and causality, date of resolution as well as treatment required, investigations needed and outcome.

The Investigator will make an assessment of whether the AE/SAE is likely to be related to treatment according to the following definitions:

Unrelated: where an event is not considered to be related to the study drug.

Possibly: although a relationship to the study drug cannot be completely ruled out, the nature of the event, the underlying disease, concomitant medication or temporal relationship make other explanations possible.

Probably: the temporal relationship and absence of a more likely explanation suggest the event could be related to the study drug.

Definitely: The known effects of the study drug or its therapeutic class, or based on challenge testing, suggest that study drug is the most likely cause.

All AEs/SAEs judged as having a reasonable suspected causal relationship (e.g. possibly, probably, definitely) to the study drug will be considered as ARs/SARs. All AEs/SAEs judged as being related (e.g. possibly, probably, definitely) to an interaction between the study drug and another drug will also be considered to be AR/SAR.

To help determine the expected nature of SAEs, appropriate Reference Safety Information (RSI) is provided in the SmPC.

The Investigators will make an assessment of severity for each AE/SAE and record this on the CRF according to one of the following categories:

Mild: an event that is easily tolerated by the participant, causing minimal discomfort and not interfering with every day activities.

Moderate: an event that is sufficiently discomforting to interfere with normal everyday activities.

Severe: an event that prevents normal everyday activities.

9.3 Recording and reporting of SAEs AND SUSARs

All SAEs / SUSARs occurring from the time of written informed consent until 14 days post cessation of trial treatment will be recorded on the SAE / SUSAR report form and faxed to the Sponsor within 24 hours of the research staff becoming aware of the event. Once all resulting queries have been resolved, the Sponsor will request the original form should also be posted to the Sponsor and a copy to be retained on site.

For each SAEs / SUSARs the following information will be collected:

- full details in medical terms and case description
- event duration (start and end dates, if applicable)
- action taken
- outcome
- seriousness criteria
- causality (i.e. relatedness to trial drug / investigation), in the opinion of the investigator
- whether the event would be considered expected or unexpected.

Any change of condition or other follow-up information will be emailed to the Sponsor as soon as it is available or at least within 24 hours of the information becoming available. Events will be followed up until the event has resolved or a final outcome has been reached.

9.4 Responsibilities

Chief Investigator/Clinical co-investigator :

Checking for AEs and ARs when participants attend for study visits.

1. Using medical judgement in assigning seriousness, causality and expectedness using the Reference Safety Information approved for the trial.
2. Using medical judgement in assigning seriousness and causality and providing an opinion on expectedness.
3. Ensuring that all SAEs and SARs (including SUSARs) are recorded and reported to the Sponsor within 24 hours of becoming aware of the event and provide further follow-up information as soon as available. Ensuring that SAEs and SARs (including SUSARs) are chased with Sponsor if a record of receipt is not received within 2 working days of initial reporting.
4. Ensuring that AEs and ARs are recorded and reported to the Sponsor in line with the requirements of the protocol.

Clinical co-investigator or independent clinical reviewer:

1. Clinical oversight of the safety of participants in the trial, including an ongoing review of the risk / benefit.
2. Using judgement in assigning seriousness, causality and expectedness of SAEs where it has not been possible to obtain local medical assessment.
3. Using judgement in assigning expectedness.
4. Immediate review of all SUSARs.
5. Review of specific SAEs and SARs in accordance with the trial risk assessment and protocol as detailed in the Trial Monitoring Plan.
6. Assigning Medical Dictionary for Regulatory Activities (MedDRA) or Body System coding to all SAEs and SARs.
7. Preparing the clinical sections and final sign off of the Development Safety Update Report (DSUR).

Sponsor:

1. Central data collection and verification of AEs, ARs, SAEs, SARs and SUSARs according to the trial protocol onto a MACRO database.
2. Reporting safety information to the CI, delegate or independent clinical reviewer for the ongoing assessment of the risk / benefit according to the Trial Monitoring Plan.

3. Reporting safety information to the independent oversight committees identified for the trial (Data Monitoring Committee (DMC) and / or Trial Steering Committee (TSC)) according to the Trial Monitoring Plan.
4. Expedited reporting of SUSARs to the MHRA and REC within required timelines.
5. Notifying Investigators of SUSARs that occur within the trial.
6. The unblinding of a participant for the purpose of expedited SUSAR reporting.
7. Checking for and notifying PIs of updates to the Reference Safety Information for the trial.
8. Preparing standard tables and other relevant information for the DSUR in collaboration with the CI and ensuring timely submission to the MHRA and REC.

Trial Steering Committee (TSC):

In accordance with the Trial Terms of Reference for the TSC, periodically reviewing safety data and liaising with the DMC regarding safety issues. See Appendix 1.

Data Monitoring Committee (DMC):

In accordance with the Trial Terms of Reference for the DMC, periodically reviewing overall safety data to determine patterns and trends of events, or to identify safety issues, which would not be apparent on an individual case basis. See Appendix 2.

9.5 Notification of deaths

Any deaths will be reported immediately to the sponsor irrespective of whether the death is thought to be related to the IMP, or an unrelated event.

9.6 Pregnancy reporting

Pregnant subjects or those trying to get pregnant will be excluded from participation but if a volunteer becomes pregnant during the course of their involvement with the trial then they will be followed (with their permission) to term.

9.7 Overdose

Several cases of overdose of Circadin have been reported post-marketing. Somnolence was the most reported adverse event. Most were mild to moderate in severity. Circadin has been administered at similar daily doses to that proposed here in clinical trials over 12 months without significantly changing the nature of the adverse reactions reported.

If a higher dose than intended is taken, which is highly unlikely, given the trial subjects, the maximum dose they would be able take if they took all their allocated tablets would be 9 x 2mg. We have reported previously that even doses of 100mg melatonin resulted in no adverse events other than mild transient drowsiness. Administration of daily doses of up to 300 mg of melatonin without causing clinically significant adverse reactions have been reported in the literature. If overdose occurs, drowsiness is to be expected. Clearance of the active substance is expected within 12h after ingestion. No special treatment is required. Any subject in whom an overdose occurred would therefore simply be monitored carefully for 24h after overdosing and an adverse event recorded.

9.8 Reporting urgent safety measures

If any urgent safety measures are taken the CI/Sponsor shall immediately and in any event no later than 3 days from the date the measures are taken, give written notice to the MHRA and the relevant REC of the measures taken and the circumstances giving rise to those measures.

9.9 The type and duration of the follow-up of subjects after adverse events.

Treatment will be stopped if a subject develops an unexpected reaction thought to be due to melatonin administration and will be followed up for 24h after the last melatonin dose. Any SUSAR related to the IMP will need to be reported to the Sponsor irrespective of how long after

IMP administration the reaction has occurred. Adverse events and reactions will be recorded for 14d after the last dose of the IMP.

9.10 Development safety update reports

The CI will provide (in addition to the expedited reporting above) DSURs once a year throughout the clinical trial, or on request, to the Ethics Committee, Host NHS Trust and Sponsor.

The report will be submitted within 60 days of the Developmental International Birth Date (DIBD) of the trial each year until the trial is declared ended.

10 STATISTICS AND DATA ANALYSIS

10.1 Sample size calculation

The number of volunteers in this pilot study is a pragmatic number and has been selected based on this being a suitable and sufficient number for a pilot study to enable determination of trial feasibility, including acceptance of the trial design by participants, and drop out rates/retention. In addition we have considered funding issues and previous studies of a similar design [8,34-36]. However, the number chosen and the cross over design will maximise the opportunity for finding any effect. We aim to recruit 32 subjects to cover losses due to drop outs and with the aim of obtaining 25 subjects who complete the protocol. This will allow an initial exploration of potential effects to enable a formal sample size to be calculated for a definitive subsequent trial. We propose that should any subject withdraw or fail to complete both arms of the trial, replacement participants will be sought if this were prior to any treament allocation. Subjects will be randomised in blocks of 8 such that of each 8 participants recruited, four will receive melatonin first and four will receive plaecbo first. The investigators and the subjects will not know the allocation; only pharmacy will know. This scheme will ensure the allocation is evenly spread over the study duration to account for any effects of seasonality.

10.2 Planned recruitment rate

Up to 2 volunteers will be recruited each week once the study has commenced. A CONSORT diagram will be provided (see Appendix 9 for template).

10.3 Statistical analysis plan

Data analysis will be simple descriptive statistics, completer analyses and basic intention to treat assessments of the intervention.

10.3.1 Summary of baseline data

Baseline data will include:
Age (numerical).
Sex (categorical).
Serum cytokine levels (numerical, continuous).
Serum melatonin and 6-hydroxymelatonin sulphate levels (numerical, continuous).
Verran and Snyder-Halpern sleep scale (numerical, continuous).
Epworth sleepiness scale (categorical, ordinal).
Data from wristband activity monitor (numerical, continuous).
Psychomotor vigilance task (numerical, continuous).
Double digit addition test (numerical, continuous).
Usual sleep habits (nominal).
Composite scale of morningness questionnaires (categorical, ordinal).

10.3.2 Primary outcome analysis

The primary outcome analysis will comprise descriptive summaries describing numbers eligible to take part, those recruited, drop outs (with reasons where possible), non-compliance, number of completers, sex distribution age distribution, type of staff (doctors or nurses), at

baseline and follow-up. The nature of this pilot study means we will not be able to feasibly stratify for sex, age, or type of staff but we will make an assessment of the influence of these possible confounders. Seasonality effects will be minimised by randomising in blocks of 8 subjects.

Summary measures will include mean and standard deviation where data are normally distributed and median and interquartile range where they are not. Paired comparisons of measures after melatonin and placebo treatments; and comparisons of baseline to after nightshift (placebo arm) will be made to explore any possible effects.

Analyses will be on an intention to treat basis, with additional analysis of 'completers' (subjects who completed the protocol and received both melatonin and placebo during two separate series of night shifts). These will provide information regarding the biochemical effectiveness of the intervention and the personal effectiveness taking into account aspects of acceptability.

Subjects will be asked to complete a questionnaire about the trial (Appendix 10) which will use a 5 point Likert scale (categorical, nominal). They will also be asked if they will consent to be contacted regarding attending focus groups after the end of the trial (see Appendix 11 for outline discussion schedule) where they will be asked to talk about aspects of the trial. This will be analysed qualitatively after transcription and identification of themes. Focus groups will not be conducted by the trial team, but by an independent qualitative researcher.

10.3.3 Secondary outcome analysis

Summary measures will include mean and standard deviation where data are normally distributed and median and interquartile range where they are not. Paired comparisons of measures after melatonin and placebo treatments; and comparisons of baseline to after nightshift (placebo arm) will be made to explore any possible effects.

10.4 Subgroup analyses

The nature of this pilot study means we will not be able to feasibly undertake subgroup analysis eg according to sex, age, or type of staff. Seasonality effects will be minimised by randomising in blocks of 8 subjects.

10.5 Adjusted analysis

The nature of this pilot study means we will not be able to feasibly stratify for sex, age, or type of staff but we will make an assessment of the influence of these possible confounders. Seasonality effects will be minimised by randomising in blocks of 8 subjects. We will not adjust for any of these effects.

10.6 Interim analysis and criteria for the premature termination of the trial

There will be no interim analysis. The blinded data will be seen by the DMC at intervals agreed as part of the DMC charter. The trial will be stopped if required by the Sponsor or DMC on safety grounds, specified as any side effects described in the SmPc which are at an unexpectedly higher incidence than previously described.

10.7 Subject population

The study population will be nurses and junior doctors (males and females) who are undertaking 2 series of night shifts within a 4-6 week period.

We will analyse on the basis of

- All-randomized population: Any subject randomized into the study, regardless of whether they received study drug and whether they completed both arms of the study
- All-treated population: Any subject randomized into the study who received at least one dose of study drug

- Protocol-compliant population: Any subject who was randomized and received the protocol required study drug exposure and required protocol processing

When considering analysis of adverse events we will compare the incidence during the melatonin arm to the placebo arm.

10.8 Procedure(s) to account for missing or spurious data

To maximise compliance and follow up, tasks and questionnaire completion before and after shifts will be undertaken with a researcher. The only task required mid shift is the ESS which takes 30 seconds to complete. We will send a text message or set an alarm for the participant to remind them. Taking the trial drug before going to bed can also be prompted by the researcher after the shift and backed up by a text message.

Missing data will not be inputted as this is a feasibility pilot trial. We will record details of missing data points where possible such as reason, where available. The focus group post trial will enable identification of any tasks etc. which participants did not like.

10.9 Other statistical considerations.

We do not anticipate any deviation from the statistical plan unless the trial is stopped prematurely.

10.11 Economic evaluation

Not applicable.

11 DATA HANDLING

11.1 Data collection tools and source document identification

Definitions of the data sources are listed in Appendix 11.

Case report forms

Physiological data will be entered into a hard copy CRF. Biochemical data will be reported to the Chief Investigator and the research team at a later date and recorded on a dedicated trial Access database. Some of the data in the CRF will be regarded as source data and will be identified as such. The investigator will keep records of all participating subjects (e.g., CRFs, samples) and all original signed informed consent forms.

11.2 Data handling and record keeping

An Access database will be used for data entry. Some data will be entered directly into the database and some will be transcribed from data in the CRF. The PVT data will be downloaded from a laptop. All data will be stored in an anonymised fashion using a unique code. The master list will be kept as hard copy only in a locked filing cabinet in a locked office in a restricted access University building. The database will be located on a University global drive in dedicated trial storage space accessible by the research team only and which is backed up daily. No identifiable data will be stored electronically. No identifiable data will be transferred electronically or otherwise. The Chief Investigator will delegate responsibility for data entry and data quality. Cross validation of data entry will be undertaken for a stated proportion of the data. Data will be analysed using SPSS v23.

11.3 Access to Data

Direct access of anonymised data will be granted to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections.

11.4 Archiving

Archiving will be authorised by the Sponsor following submission of the end of study report. All trial documents will be archived according to usual practice for a minimum of 10 years after completion of trial.

12 MONITORING, AUDIT & INSPECTION

A Trial Monitoring Plan will be developed by NHS Grampian and agreed by the Trial Management Group (TMG) and TSC based on the trial risk assessment which may include on site monitoring. Monitoring will be undertaken at study initiation and at six monthly intervals thereafter until study end.

13 ETHICAL AND REGULATORY CONSIDERATIONS

13.1 Research Ethics Committee (REC) review and reports

Before the start of the trial, approval will be sought from a REC for the trial protocol, informed consent forms and other relevant documents e.g. advertisements and GP information letters. Substantial amendments that require review by REC will not be implemented until the REC grants a favourable opinion for the study. All correspondence with the REC will be retained in the Trial Master File/Investigator Site File. An annual progress report (APR) will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended. The Chief Investigator will notify the REC of the end of the study. If the study is ended prematurely, the Chief Investigator will notify the REC, including the reasons for the premature termination. Within one year after the end of the study, the Chief Investigator will submit a final report with the results, including any publications/abstracts, to the REC.

13.2 Peer review

The trial proposal was reviewed as part of the grant awarding process. The Trial Steering Group and Data Monitoring Committee will see and approve the contents of the protocol prior to commencement of the study. The data from the study will be peer reviewed as part of the publication process.

13.3 Public and Patient Involvement

The proposed trial was reviewed by the Grants Committee of the National Institute of Academic Anaesthesia which includes lay representation. After completion of the trial we will ask subjects to complete a questionnaire (Appendix 11) and also ask for further consent to contact participants at a later date regarding taking part in focus groups to tell us their views about aspects of the trial (Appendix 12).

13.4 Regulatory Compliance

The protocol and trial conduct will comply with the Medicines for Human Use (Clinical Trials) Regulations 2004 and any relevant amendments. The trial will also not commence until management approval has been granted by NHS Grampian R&D department.

13.5 Protocol compliance

Any changes in research activity, except those necessary to remove an apparent, immediate hazard to the participant, will be reviewed and approved by the Sponsor. Amendments to the protocol will be submitted in writing to the appropriate REC, Regulatory Authority and local R&D for approval prior to participants being enrolled into an amended protocol.

The Chief Investigator will not implement any deviation from the protocol without agreement from the appropriate REC, Regulatory Authority and R&D except where necessary to eliminate an immediate hazard to trial participants. In the event that a deviation from the protocol is required, the nature of and reasons for the deviation will be recorded in the CRF. If this

necessitates a subsequent protocol amendment, this should be submitted to the REC, Regulatory Authority and local R&D for review and approval if appropriate.

13.6 Notification of Serious Breaches to GCP and/or the protocol

The Sponsor will be notified immediately by the CI of any case where the safety or physical or mental integrity of the subjects of the trial, or the scientific value of the trial are likely to be affected to any degree (ie a serious breach). The Sponsor will notify the licensing authority in writing of any serious breach of the conditions and principles of GCP in connection with the trial, or the protocol relating to that trial, as amended from time to time, within 7 days of becoming aware of that breach as per the Standard Operating Procedure for reporting of serious breaches.

13.7 Data protection and patient confidentiality

All investigators and trial site staff will comply with the requirements of the Data Protection Act 1998 with regards to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles.

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain participant confidentiality. All records will be kept in a locked filing cabinet in a locked office. Data will not be released without the written permission of the participant, except as necessary for monitoring and auditing by the Sponsor, its designee, Regulatory Authorities, or the REC. The Investigator and study site staff involved with this study will not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the Sponsor or its designee will be obtained for the disclosure of any said confidential information to other parties.

All data will be anonymised by the Chief Investigator or a delegated member of the research team using a unique code. The master list will be kept as hard copy only in a locked filing cabinet in a locked office in a restricted access University building. The database will be located on a University global drive in dedicated trial storage space accessible by the research team only and which is backed up daily. No identifiable data will be stored electronically. No identifiable data will be transferred electronically or otherwise. Only the direct research team will have access to these files. Professor Helen Galley is data custodian. Data will be kept for the stipulated period of time.

Published results will not contain any personal data that could allow identification of individual participants.

13.8 Financial and other competing interests for the chief investigator, PIs at each site and committee members for the overall trial management

Any financial and other competing interests of the researchers will be documented and kept in the TMF.

13.9 Indemnity

Indemnity will be via the University of Aberdeen trial insurance. Certificate copy will be held in the TMF.

13.10 Amendments

The sponsor may make a non-substantial amendment at any time during a trial. If the sponsor wishes to make a substantial amendment to the REC application or the supporting documents, the sponsor must submit a valid notice of amendment to the REC for consideration. The REC will provide a response regarding the amendment within 35 days of receipt of the notice. It is the sponsor's responsibility to decide whether an amendment is substantial or non-substantial for the purposes of submission to the REC. Amendments will also be notified to the NHS R&D department to assess whether the amendment affects the NHS permission.

13.11 Post trial care

Melatonin or Circadin™ will not be prescribed for study participants at the end of the trial.

13.12 Access to the final trial dataset

Professor H Galley, Professor N Webster, Dr L Aucott and Ms Bensita Thottakam will have access to the final dataset and will be responsible for data analysis and preparation of the data for publication.

14 DISSEMINIATION POLICY

14.1 Dissemination policy

The data obtained from the trial will belong to the researchers. Data will be analysed and prepared for dissemination at relevant scientific meetings and journals. Trial progress and a final report will be placed on a trial web site to which the participants will have access.

In addition the trial protocol will be placed in a publically accessible site prior to study start.

14.2 Authorship eligibility guidelines and any intended use of professional writers

Ownership of the data arising from this study resides with the study team. On completion of the study, the study data will be analysed and tabulated, and a study report will be prepared. The study report will be used for publication and presentation at scientific meetings. Investigators have the right to publish orally or in writing the results of the study. The authors of the publications will be those who fulfill the authorship criteria defined by the The International Committee of Medical Journal Editors.

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16. APPENDICIES

16.1 APPENDIX 1

Trial steering committee (draft) charter

Introduction

The role of the Trial Steering Committee (TSC) is to provide oversight for the MIDNIGHT study on behalf of the Trial Sponsor and the Trial Funder and to ensure that the trial is conducted according to the guidelines for Good Clinical Practice (GCP), Research Governance Framework for Health and Social Care and all relevant regulations and local policies.

The purpose of this document is to define the roles and responsibilities of the TSC and to guide its activities, its relationship with other trial committees, its membership, and the format, purpose and timings of its meetings. The charter also describes the procedures for ensuring confidentiality and proper communication to and from the TSC and an outline of the content of the reports to be provided to the TSC.

Terms of reference

- To provide advice, through its Chair, to the Trial Management Group (TMG) on the conduct of the study.
- To oversee the progress of the trial towards its overall objectives and adherence to the protocol.
- To provide advice, suggest or agree proposals for substantial protocol amendments based on information from the Data and Safety Monitoring Committee (DMC). The DMC does not make decisions on the trial, but makes recommendations to the TSC which then reports to the Sponsor and TMG as appropriate.

Membership and Primary responsibilities of the TSC

The MIDNIGHT TSC will be a multidisciplinary group comprising of the following members who jointly have responsibility for the design, conduct and evaluation of the clinical research project.

- An independent Chair (Dr Alison Pittard, Leeds)
- Chief Investigator, Professor Helen Galley and co-investigator Professor Nigel Webster who together with the trial statistician (Dr Lorna Aucott) form the Trial Management Group
- Independent clinician with relevant experience: (Dr Paul Holder).
- Lay representative: (Mrs Sophie Welch).

The responsibility for calling and organising TSC meetings lies with the Chief Investigator in association with the Chair. The Chair assisted by the Chief Investigator is responsible for facilitating the meetings and summarising discussions. The Chair will approve the appointment of the members of the TSC at the first meeting.

The TSC membership is for the duration of the trial. If any members leave the TSC, the TMG will provide replacements promptly for appointment by the Chair. It is expected that the TSC will meet at least annually. Meetings can take any format.

Interaction between TSC and other study committees

The DMC will report any safety concerns to the TSC, making recommendations to the TMG and Sponsor via reports to the TSC.

Agreements

TSC members should formally register their agreement to be a member of the committee as well as their agreement with the contents of the charter, trial confidentiality and should declare any potential conflicts of interest.

Independent members should complete and return the signed agreement and competing interests form provided.

Responsibilities

The TSC on behalf of the Sponsor and Funder will have overall responsibility for the design and conduct of the trial and for safeguarding the rights, safety and well being of participants. Responsibilities of the TSC to include:

- Reviewing recruitment/retention of participants and their management
- Reviewing study protocol and other study documentation.
- Determine if amendments to the protocol or changes to study conduct are required and deciding on changes to these and to study conduct in general. Any changes to trial documentation or conduct must be notified to the TSC. Any changes will first have been approved by the Sponsor.
- Reviewing adherence to the protocol
- Assessing the impact and relevance of external evidence
- Monitoring the overall conduct of the trial, ensuring that it follows the standards set out in the guidelines of GCP, assessing the safety and efficacy of the interventions, recruitment figures and completion of trial assessments.
- Reviewing, commenting and making decisions on extension requests.
- Reviewing the recommendations of the DMC (if applicable) and suggesting appropriate action to the TMG
- Monitoring the progress of the trial and deciding on appropriate action in order to maximise the chances of completing it within the agreed timelines.
- Considering new information relevant to the study e.g. results from other studies that may have a bearing to the conduct of the study and deciding on appropriate action.
- Endorsing the annual report to the funder (if required)

The TSC may recommend acting upon safety concerns raised by the DMC such as early termination of the trial or modification of the study design.

The TSC will be available to provide independent advice as required not just when meetings are scheduled.

The TSC swill maintain confidentiality of all information it receives.

Members will not discuss confidential issues from their involvement in the study until the primary results have been published.

Role of the TSC Chair

- Arrange the first meeting of the TSC with the assistance of the CI to agree contents of charter and set up schedule of meetings
- Establish clear reporting lines
- Become familiar with the role of the DMC
- Provide an independent, experienced opinion if conflicts arise between the needs of the research team, the Funder, the Sponsor and/or any other agencies
- Leading the TSC to provide regular, impartial oversight of the trial, especially to identify and pre-empt problems
- Ensuring that changes to the protocol are debated and endorsed by other members of the TSC

For decisions to be made, at least 2 independent members of the TSC should be present (including the Chair), the CI and another representative from the TMG.

TSC meetings

- The responsibility for calling and organising a TSC meeting lies with the CI in association with the TSC Chair.
- Professor Galley will organise the meetings as requested. Meetings will be in person or by teleconference as preferred by the Chair
- All TSC members will be provided with study documents and a report prior to the meeting.
- The first TSC meeting will discuss, revise and finalise the terms of reference, agree the content of the TSC charter and sign any declaration, and agree the frequency of the meetings.
- The timings of the meeting will be clarified by the Chair after the first meeting and meetings can also be held at any time at the request of the CI or TSC chair
- The final TSC meeting will be arranged when target recruitment is completed, all data collected and cleaned and the database is locked. This final meeting will be held to discuss completed data and interpretation, and publication timelines. If the study is terminated prematurely, no final study meeting is required.

Attendance

Every effort will be made to ensure that all TSC members can attend the meetings. The CI must try to attend all meetings, especially if major actions are expected.

At least 2 independent members of the TSC should be present (including the Chair), the CI and another representative from the TMG. If the TSC is considering major actions the TSC Chair should communicate with absent members, including the CI, as soon after the meeting as possible to determine whether they all agree. If there is disagreement amongst absent members a further meeting should be arranged with the full TSC.

Reporting

Prior to a TSC meeting a report will be prepared by the TMG and circulated to TSC members at least a week before the meeting.

On consideration of the information presented at these meetings, the TSC will provide recommendations of appropriate action in writing to the TMG who will be responsible for implementing any actions. The TSC will also provide feedback to the DMC and to the Sponsor, via the TMG.

Minutes of the meeting including key points and actions will be prepared by a member of the TMG. These minutes will describe the proceedings and include the recommendations of the TSC. All members of the TSC must agree the minutes and these will be signed off by the TSC Chair on behalf of all members. Minutes will be circulated to all TSC members, the TMG and the Sponsor. Approved Minutes will be filed in the Trial Master File.

Decisions and recommendations by the TSC will be where possible, unanimous; if not a vote may be taken. The role of the Chair is to summarise discussions and encourage consensus. Therefore it is best for the chair to give his/her own opinion last. It is important that the implications (ethical, practical and financial) for the trial be considered before any decision is made.

Contents of the TSC Reports

An outline of the contents of the TSC report is given below:

- Any protocol amendments

- Patient screening and any eligibility violations
- Protocol violations
- Study accrual by month/total
- Completeness and quality of data collected
- CRF return, entry into database
- Baseline characteristics
    - Demographics
- Any matters affecting the trial
- Latest DMC report and recommendations

Conflicts of interest

TSC members will not have any apparent financial, scientific or intellectual conflict of interest that could prevent them from objectively reviewing the study protocol, interim and final data and giving advice to the TMG. TSC members should disclose to the Chair any other conflicts they consider relevant. Any members who develop significant conflicts of interest during the course of the trial should resign from the TSC.

Publication

Manuscripts that arise from the trial will be shared with the TSC and members will be able to comment. The TSC members and their affiliations will be acknowledged in reports of the trial.

16.2 APPENDIX 2

Data monitoring and safety committee draft charter

1. Introduction	
Name (and sponsor's ID) of trial plus ISRCTN and/or EUDRACT number	MIDNIGHT EudraCT: 2015-004106-42 Sponsor's ID: 3-047-15
Objectives of trial	MIDNIGHT is a pilot Phase II study in ICU staff working night shifts. The aim is to investigate the feasibility of this trial design to assess the effects of exogenous melatonin (Circadin) compared to placebo in staff working night shifts on the intensive care unit (ICU) and the most appropriate endpoint measures for future studies. This is a pilot study- there are no previous data on which to base a sample size calculation. We will explore effects of Circadin on sleeping patterns, psychomotor vigilance and biochemical measures and on the transcriptome. The various measures of sleep will include quality, latency, disturbance, and sleepiness. Psychomotor function will be assessed using reaction time testing and double digit addition tasks. Cytokine profiles, melatonin and 6-hydroxymelatonin concentrations and gene transcripts will be measured. Since much of these data have not been reported in people actually working night shifts, this study will generate important data even in the absence of any effect of Circadin, which is unlikely.
Outline of scope of charter	The purpose of this document is to describe the roles and responsibilities of the independent DMC for the trial, including the timing of meetings, methods of providing information to and from the DMC, frequency and format of meetings, statistical issues and relationships with other committees.
2. Roles and responsibilities	
The aims of the committee	To protect and serve MIDNIGHT trial participants (especially safety) and to assist and advise the Investigators so as to protect the validity and credibility of the trial. To safeguard the interests of trial participants, assess the safety and efficacy of the interventions during the trial, and monitor the overall conduct of the clinical trial.
Terms of reference	The DMC will receive and review the progress and accruing data of this trial and provide advice on the conduct of the trial. The DMC will inform the Sponsor if, in their view: (i) the results are likely to convince a broad range of clinicians, including those supporting the trial and the general clinical community, that one trial arm is clearly indicated or contraindicated, and there was a reasonable expectation that this new evidence would materially influence patient management or (ii) it becomes evident that no clear outcome would be obtained.
Specific roles of the DMC	Interim review of the trial's progress including updated figures on recruitment, data quality, and main outcomes and safety data. A selection of specific aspects could be compiled from the following list:- • assess data quality, including completeness (and by so doing encourage collection of high quality data) • monitor recruitment figures and losses to follow-up • monitor compliance with the protocol by participants and

	investigators • comment on trial conduct – organisation and implementation of trial protocol • monitor evidence for treatment harm (eg SAEs) • decide whether to recommend that the trial continues to recruit participants or whether recruitment should be terminated either for everyone or for some participant subgroups • suggest additional data analyses • advise on protocol modifications suggested by investigators or sponsors (eg to inclusion criteria, trial endpoints, or sample size) • monitor continuing appropriateness of patient information • monitor compliance with previous DMC recommendations • consider the ethical implications of any recommendations made by the DMC • assess the impact and relevance of external evidence
3. Before or early in the trial Input to the Protocol	All potential DMC members will have sight of the protocol before agreeing to join the committee. Before recruitment begins the trial will have undergone review by the funder and sponsor, scrutiny by other trial committees and a research ethics committee. DMC members will be independent and constructively critical of the ongoing trial, but also supportive of aims and methods of the trial.
	The DMC will meet early in the course of the trial, to discuss the protocol, the trial, any analysis plan, future meetings, and to have the opportunity to clarify any aspects with the principal investigators.
Specific regulatory issues	A favourable REC approval and NHS R&D management permission is required. Note: this study is a **not** a CTIMP and does **not** require a Clinical Trial Authorisation from the MHRA.
Issues specific to the treatment under study	Melatonin has been used at high oral doses (over 100mg) in several disease conditions and has been given to healthy subjects. Circadin (slow release melatonin will be used off licence in this trial.
Confirmation of agreement with this Charter	DMC members will formally register their assent by confirming (1) that they agree to be on the DMC and (2) that they agree with the contents of this Charter.
4. Composition Membership and size of the DMC	Membership of the DMC will comprise at least one clinician experienced in the clinical area and at least one statistician. The members will be independent of the trial (eg should not be involved with the trial in any other way or have some competing interest that could impact on the trial). Any competing interests, both real and potential, should be declared. A short competing interest form should be completed and returned by the DMC members to the trial co-ordinating centre. The members of the DMC for this trial are: (1) Dr Andy Cohen (Chair, Leeds) (2) Professor Peter Andrews (Edinburgh). (3) Dr Malachy Columb (statistical advisor).
The Chair's role.	The Chair (Dr A Cohen) will have previous experience of serving on DMCs and experience of chairing meetings, and will facilitate and summarise discussions.
The responsibilities of the DMC statistician	The DMC membership will include a mamber who can provide independent statistical expertise (Dr M Columb).

The responsibilities of the trial statistician	The trial statistician, Dr Lorna Aucott will produce (or oversee the production of) the report to the DMC and will participate in DMC meetings, guiding the DMC through the report, participating in DMC discussions.
The responsibilities of the Chief and Principal Investigators	The Investigators will be available to attend open sessions of the DMC meeting if asked.
5. Relationships	
DMC is advisory	The DMC does not make decisions about the trial, but rather makes recommendations to the Sponsor and Chief Investigator.
Payments to DMC members	Members will be reimbursed for travel if required.
Disclosure of competing interests	Competing interests will be disclosed. These are not restricted to financial matters – involvement in other trials or intellectual investment could be relevant. Although members may well be able to act objectively despite such connections, complete disclosure enhances credibility. DMC members will not use interim results to inform trading in pharmaceutical shares, and careful consideration should be given to trading in stock of companies with competing products.
6. Organisation of DMC meetings	
Expected frequency of DMC meetings	The exact frequency of meetings will depend upon pre-specified plans, and on trial events. The wishes of the DMC and needs of the Sponsor will be considered when planning each meeting. It is recommended that the DMC meet at least yearly.
Meetings format	Meetings will be a combination of face to face, video- or tele-conference depending on the DMC Chair's preference and circumstances.
Organisation of DMC meetings	Meetings will comprise a mixture of open and closed sessions. Closed meetings will comprise the DMC and Trial Statistician as required and Open will involve these and the Investigators, Sponsor representative or other personnel if requested by the DMC.
7. Trial documentation and procedures to ensure confidentiality and proper communication	
Intended content of material to be available in open sessions	Open sessions: Accumulating information relating to recruitment and data quality (eg data return rates, treatment compliance) will be presented. Toxicity details based on pooled data will be presented and total numbers of events for the primary outcome measure and other outcome measures may be presented, at the discretion of the DMC.
Intended content of material to be available in closed sessions	Closed sessions: In addition to all the material available in the open session, the closed session material will include safety data by treatment group. No unblinded data will be provided unless for safety reasons.
Blinding	Blinding will be maintained unless there is an issue when data will be unblinded if requested by the DMC.
Who will see the accumulating data and interim analysis	The people who will see the accumulating data will be specified by the DMC Chair. There is no interim data analysis planned. DMC members do **not** have the right to share confidential information with anyone outside the DMC, including the Chief Investigator.
Identification and circulation of external evidence (eg from other trials/ systematic reviews)	Identification and circulation of external evidence will be the responsibility of the Trial team.

Communication of decisions/ recommendations that are reached	The DMC will report its recommendations in writing to the Sponsor's representative. This will be copied to the trial statistician. The report from the DMC may include a summary paragraph suitable for trial promotion purposes.
After the meeting	The DMC members will store the papers safely after each meeting so they may check the next report against them. After the trial is reported, the DMC members will destroy all interim reports.
8. Decision making	
Recommendations available to the DMC	Possible recommendations could include:- • No action needed, trial continues as planned • Early stopping due, for example, to clear benefit or harm of a treatment, futility, or external evidence • Extending recruitment (based on actual control arm response rates being different to predicted rather than on emerging differences) or extending follow-up • Sanctioning and/or proposing protocol changes
Rules or guidelines	The DMC will review and agree any interim analysis plan. Reasons will be recorded for disregarding a stopping guideline.
How decisions or recommendations will be reached within the DMC	• The decision making methods and criteria that will be adopted for guiding deliberations will be pre-defined • The process of decision making, including whether there will be voting or other formal methods of achieving consensus will be defined. The method of deliberation should not be revealed to the overseeing committee as this may reveal information about the status of the trial's data. • The role of the Chair - to summarise discussions and encourage consensus; it may be best for the Chair to give their own opinion last. If the DMC cannot achieve a unanimous decision this, a vote may be taken. It is important that the implications (eg ethical, statistical, practical, financial) for the trial be considered before any recommendation is made.
When the DMC is quorate for decision-making	All members should attend. Members who cannot attend in person should be encouraged to attend by teleconference. If, at short notice, any DMC members cannot attend at all then the DMC may still meet if at least one statistician and one clinician, including the Chair will be present. If the DMC is considering recommending major action after such a meeting the DMC Chair should talk with the absent members as soon after the meeting as possible to check they agree. If they do not, a further teleconference should be arranged with the full DMC.
DMC members who cannot attend the meeting may still input	If the report is circulated before the meeting, DMC members who will not be able to attend the meeting may pass comments to the DMC Chair for consideration during the discussions.
Members who do not attend meetings	If a member does not attend a meeting, it should be ensured that the member is available for the next meeting. If a member does not attend a second meeting, they should be asked if they wish to remain part of the DMC. If a member does not attend a third meeting, they should be replaced.
9. Reporting	
To whom will the DMC report their recommendations/decisions, and in what form	This will be by email letter to the Sponsor's representative. A timescale will be specified.

Minutes	Separate records may be required for open and closed sessions. The DMC Chair should sign off any minutes or notes.
Disagreement between the DMC and the body to which it reports	If the DMC has serious problems or concerns with the Sponsor's decision a meeting of these groups should be held. The information to be shown would depend upon the action proposed and the DMC's concerns. Depending on the reason for the disagreement confidential data will often have to be revealed to all those attending such a meeting. The meeting will be chaired by someone not directly involved with the trial.
10. After the trial	
Publication of results	At the end of the trial there will be a meeting to allow the DMC to discuss the final data with investigators/sponsors and give advice about data interpretation.
Information about the DMC in published trial reports	DMC members will be named and their affiliations listed in the main report, unless they explicitly request otherwise. A brief summary of the timings and conclusions of DMC meetings will be included in the body of this paper.
Approval of publications by the DMC	The DMC will be given the opportunity to read and comment on any publications before submission.
After the trial has been published	The DMC may discuss issues from their involvement in the trial when permission is agreed with the Sponsor.

16.3 APPENDIX 3

Risk assessment

Risks associated with trial interventions

☒ LOW ≡ Comparable to the risk of standard medical care

☐ MODERATE ≡ Somewhat higher than the risk of standard medical care

☐ HIGH ≡ Markedly higher than the risk of standard medical care

The study represents use of a licensed product with an established safety profile in a subject population outside of that licence and indication, in healthy subjects. The safety and efficacy of melatonin has been studied in populations of similar age to those we are studying (>18) and in paediatric populations (to manage sleep disturbance in children with neurodevelopmental disorders). The study has been classified by the MHRA as **not** a CTIMP.

In cases of overdose excessive drowsiness is the only likely risk (and if all tablets were taken simultaneously the total dose a subject would be exposed to is lower than the 300mg the SmPC covers in overdose). Any drowsiness would be expected to rapidly resolve as melatonin is rapidly cleared.

The dose to be used is based on two other studies of healthy subjects (airline crew) by Paul and colleagues where 6mg Circadin was used (Sleep-inducing pharmaceuticals: a comparison of melatonin, zaleplon, zopiclone, and temazepam. Aviat Space Environ Med 2004; 75: 512-9 and Impact of melatonin, zaleplon, zopiclone, and temazepam on psychomotor performance. Aviat Space Environ Med 2003; 74: 1263-70) with no side effects other than drowsiness.

What are the key risks related to therapeutic interventions you plan to monitor in this trial?		How will these risks be minimised?		
Intervention	**Body system/Hazard**	**Activity**	**Frequency**	**Comments**
Circadin™ or placebo	Drowsiness	Driving/operating machinery	Common	Subjects will take trial drug only when they have reached home and will be advised not to drive or operate machinery should they feel drowsy.

Project management team DMC and TSC in place. Reputational risk- independently peer reviewed as part of funding process.

16.4 APPENDIX 4

Screening questionnaire

1. What is your weight? ……Kg
2. What is your height? ……..cm
3. Male / female
4. Age……years

Female participants only

5. Please confirm that
   - You are not pregnant or breastfeeding **Yes/No**
   - And are not trying to become pregnant **Yes/No**

6. Please also confirm that at least one of the following applies to you **Yes/No**
   - You are using reliable contraception (and will continue to do so) *OR*
   - You are post-menopausal *OR*
   - You have been sterilised *OR*
   - You are not sexually active *OR*
   - You are infertile

All participants

7. Have you any chronic health problems? **Yes/No**
8. Are you taking any medication (other than oral contraceptives)? **Yes/No**
9. Do you smoke? **Yes/No**
10. Do you use sedatives/sleeping pills/anti-histamines/herbal sleeping remedies? **Yes/No**

16.5 APPENDIX 5

Usual sleep habits questionnaire

1. On workdays (dayshift), I usually go to bed at: _____
2. On workdays, the earliest time in the last 2 weeks I have gone to bed is: _____
3. On workdays, the latest time in the last 2 weeks I have gone to bed is: _____
4. My usual weekend (non-work days) bedtime is: _____
5. On workdays, I wake up at: _____
6. On weekends (non-work) days, I wake up at: _____
7. To feel my best, I should go to bed at: _____
8. To feel my best, I should get up at: _____
9. In the evening, I usually start feeling tired at: _____
10. The amount of time that I usually take to fall asleep is: _____
11. I wake up naturally / use an alarm.
12. I take a nap about _____ days each week.
13. After taking a nap, I usually feel: refreshed / groggy / sleepy.

16.6 APPENDIX 6

The Epworth Sleepiness Scale

How likely are to doze off or fall asleep in the following situations, in contrast to feeling just tired? This refers to how you would feel if you were in the situation NOW. Use the following scale to choose the most appropriate number for each situation:

0 = would never doze

1 = slight chance of dozing

2 = moderate chance of dozing

3 = high chance of dozing

Situational chance of dozing

Sitting and reading	0	1	2	3
Watching TV	0	1	2	3
Sitting, inactive in a public place	0	1	2	3
As a car passenger for an hour	0	1	2	3
Lying down to rest in the afternoon when circumstances permit	0	1	2	3
Sitting and talking to someone	0	1	2	3
Sitting quietly after a lunch without alcohol	0	1	2	3
In a car, while stopped for a few minutes in the traffic	0	1	2	3

Higher score = more sleepy

From : Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep* 1991; 14 :540-5

16.7 APPENDIX 7

COMPOSITE SCALE OF MORNINGNESS

Please circle the response for *each* item that best describes *you*.

1. **Considering only your own "feeling best" rhythm, at what time would you get up if you were entirely free to plan your day?**

   5:00-6:30 a.m. (5)

   6:30-7:45 a.m. (4)

   7:45-9:45 a.m. (3)

   9:45-11:00 a.m. (2)

   11:00 a.m.-12:00 (noon) (1)

2. **Considering your only "feeling best" rhythm, at what time would you go to bed if you were entirely free to plan your evening?**

   8:00-9:00 p.m. (5)

   9:00-10:15 p.m. (4)

   10:15 p.m.-12:30 a.m. (3)

   12:30 a.m.-1:45 a.m. (2)

   1:45 a.m.-3:00 a.m. (1)

3. **Assuming normal circumstance, how easy do you find getting up in the morning?**

   Not at all easy (1)

   Slight easy (2)

   Fairly easy (3)

   Very easy (4)

4. **How alert do you feel during the first half hour after having awakened in the morning?**

   Not at all alert (1)

   Slightly alert (2)

   Fairly alert (3)

   Very alert (4)

5. **During the first half hour after having awakened in the morning, how tired do you feel?**

   Very tired (1)

   Fairly tired (2)

   Fairly refreshed (3)

   Very refreshed (4)

6. **You have decided to engage in some physical exercise. A friend suggests that you do this one hour twice a week and the best time for him is 7:00-8:00 a.m. Bearing in mind nothing else but your own "feeling best" rhythm, how do you think you would perform?**

   Would be in good form (4)

   Would be in a reasonable form (3)

   Would find it difficult (2)

   Would find it very difficult (1)

7. **At what time in the evening do you feel tired and, as a result, in need of sleep?**

   8:00-9:00 p.m. (5)

   9:00-10:15 p.m. (4)

   10:15 p.m.-12:30 a.m. (3)

   12:30 a.m.-1:45 a.m. (2)

   1:45 a.m.-3:00 a.m. (1)

8. **You wish to be at your peak performance for a test which you know is going to be mentally exhausting and lasting for two hours. You are entirely free to plan your day, and considering only you own "feeling best" rhythm, which ONE of the four testing times would you choose?**

   8:00-10:00 a.m. (4)

   11:00 a.m. - 1:00 p.m. (3)

   3:00-5:00 p.m. (2)

   7:00-9:00 p.m. (1)

9. **One hears about "morning" and "evening" types of people. Which ONE of these types do you consider yourself to be?**

   Definitively a morning type (4)

   More a morning than an evening type (3)

   More an evening than a morning type (2)

   Definitively an evening type (1)

10. **When would you prefer to rise (provided you have a full day's work - 8 hours) if you were totally free to arrange your time?**

    Before 6:30 a.m. (4)

    6:30-7:30 a.m. (3)

    7:30-8:30 a.m. (2)

    8:30 a.m. or later (1)

11. **If you always had to rise at 6:00 a.m., what do you think it would be like?**

    Very difficult and unpleasant (1)

    Rather difficult and unpleasant (2)

    A little unpleasant but no great problem (3)

    Easy and not unpleasant (4)

12. How long a time does it usually take before you "recover your senses" in the morning after rising from a night's sleep?

0-10 minutes (4)

11-20 minutes (3)

21-40 minutes (2)

more than 40 minutes (1)

13. Please indicate to what extent you are a morning or evening *active* individual.

Pronounced morning active (morning alert and evening tired) (4)

To some extent, morning active (3)

To some extent, evening active (2)

Pronounced evening active (morning tired and evening alert) (1)

Scores are in brackets after each question. A score of 22 or less indicates an 'evening type'; a score of 44 or more indicates a 'morning type' and a score in between is classed as 'indeterminate'.

From: Smith CS, Reilly C, Midkiff K Evaluation of three circadian rhythm questionnaires with suggestions for an improved measure of morningness. *J Appl Psychol* 1989; 74: 728-38

16.8 APPENDIX 8

VSH Sleep Scale

Directions:

Answer each question by placing a vertical mark across the answer line at the point which BEST REFLECTS YOUR OPINION.

Example: Happy _____|_____ Sad

Answer all of the following questions about **last night's sleep** and **during the day yesterday**. Consider the night's sleep to begin from the time you first tried to go to sleep to the time you were finally "up" in the morning.

Example: subject marks across a 10cm line as appropriate

1.	Did not wake during the night	_____	Was awake ten hours
2.	Had no sleep at all	_____	Excluding time awake, had ten hours of sleep

Sleep scale analysis domains

1.	Did not wake during the night	DISTURBANCE Wake after sleep onset (WASO)	Was awake ten hours
2.	Had no sleep at all	EFFICIENCY Total sleep time (TST)	Excluding time awake, had ten hours of sleep
3.	Did not sleep during the day yesterday	SUPPLEMENTATION Daytime sleep (DTS)	Slept ten hours during the day
4.	Did not sleep yesterday morning	SUPPLEMENTATION AM sleep (AMS)	Slept off and on yesterday morning

5.	Did not sleep yesterday evening	SUPPLEMENTATION PM sleep (PMS)	Slept off and on yesterday evening
6.	Fell asleep immediately	DISTURBANCE Sleep latency (SL)	Did not fall asleep
7.	Slept lightly	DISTURBANCE Soundness of sleep (SS)	Slept deeply
8.	Had no trouble with disrupted sleep	DISTURBANCE Quality of disturbance (QD)	Had a lot of trouble with disrupted sleep
9.	Didn't wake at all	DISTURBANCE Mid sleep awakening (MSA)	Was awake off and on all night
10.	Had no trouble falling asleep	DISTURBANCE Quality of latency (QL)	Had a lot of trouble falling asleep
11.	Didn't move last night	DISTURBANCE Movement during sleep (MDS)	Tossed all night
12.	Awoke exhausted	EFFICIENCY Rest upon awakening (RUA)	Awoke refreshed
13.	After I woke in the morning I stayed awake	SUPPLEMENTATION wake after final arousal (WAFA)	After morning awakening, dozed off and on
14.	Had a bad night's sleep	EFFICIENCY Subjective quality of sleep (SQS)	Had a good night's sleep
15.	Had enough sleep	EFFICIENCY Sleep sufficient evaluation (SSE)	Did not have enough sleep

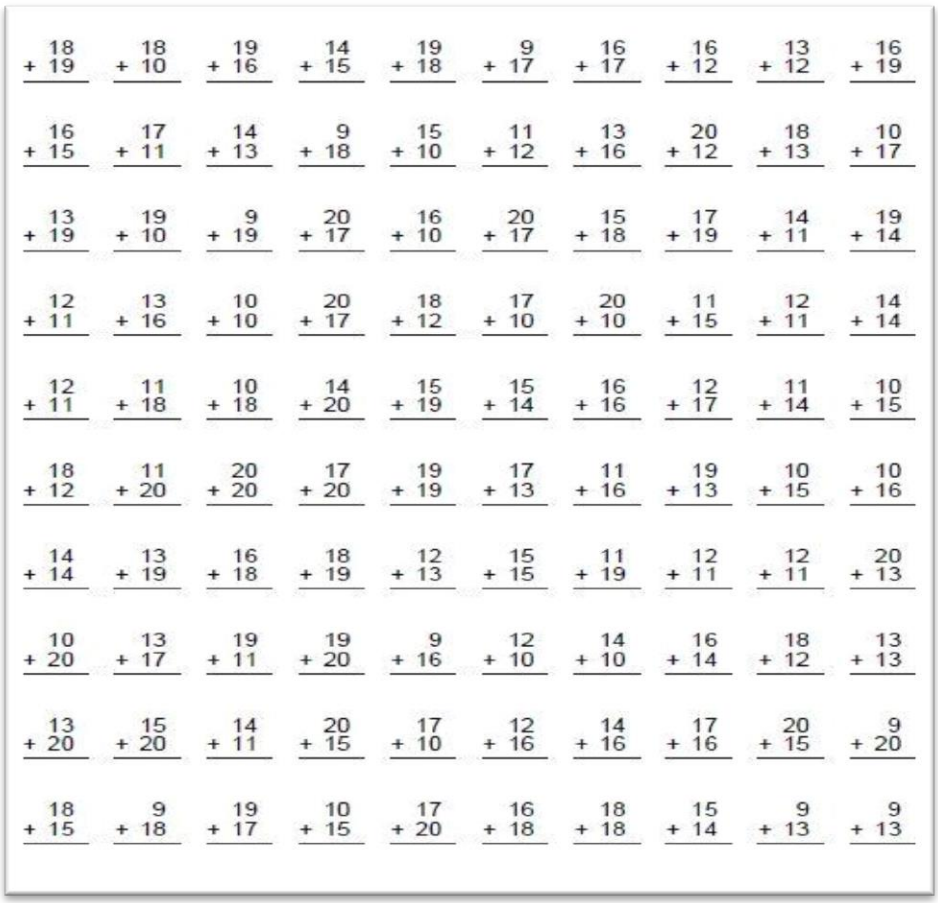
Total sleep period = TST + WASO

From: Snyder-Halpern R, Verran JA. Instrumentation to describe subjective sleep characteristics in healthy subjects. *Res Nurs Health* 1987;10: 155–63

16.9 APPENDIX 9

Double digit addition test worksheet example

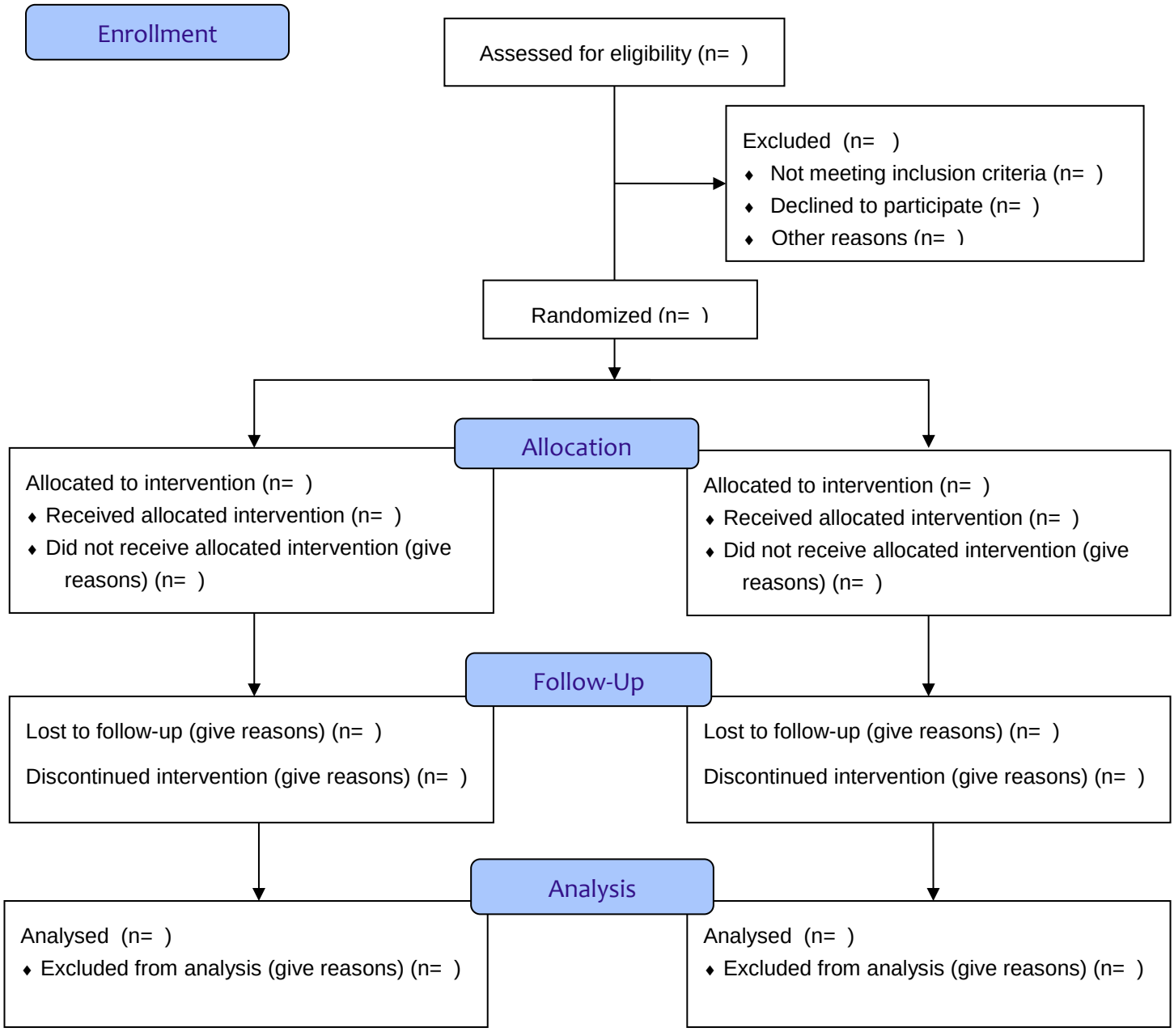
[to be added]



18 + 19	18 + 10	19 + 16	14 + 15	19 + 18	9 + 17	16 + 17	16 + 12	13 + 12	16 + 19
16 + 15	17 + 11	14 + 13	9 + 18	15 + 10	11 + 12	13 + 16	20 + 12	18 + 13	10 + 17
13 + 19	19 + 10	9 + 19	20 + 17	16 + 10	20 + 17	15 + 18	17 + 19	14 + 11	19 + 14
12 + 11	13 + 16	10 + 10	20 + 17	18 + 12	17 + 10	20 + 10	11 + 15	12 + 11	14 + 14
12 + 11	11 + 18	10 + 18	14 + 20	15 + 19	15 + 14	16 + 16	12 + 17	11 + 14	10 + 15
18 + 12	11 + 20	20 + 20	17 + 20	19 + 19	17 + 13	11 + 16	19 + 13	10 + 15	10 + 16
14 + 14	13 + 19	16 + 18	18 + 19	12 + 13	15 + 15	11 + 19	12 + 11	12 + 11	20 + 13
10 + 20	13 + 17	19 + 11	19 + 20	9 + 16	12 + 10	14 + 10	16 + 14	18 + 12	13 + 13
13 + 20	15 + 20	14 + 11	20 + 15	17 + 10	12 + 16	14 + 16	17 + 16	20 + 15	9 + 20
18 + 15	9 + 18	19 + 17	10 + 15	17 + 20	16 + 18	18 + 18	15 + 14	9 + 13	9 + 13

16.10 APPENDIX 10

CONSORT Flow Diagram Template



16.11 APPENDIX 11

Post trial questionnaire

Please circle your answers.

1. **The trial was well organised**

Strongly agree Agree Ambivalent Disagree Strongly disagree

2. **Communication with the researchers was good**

Strongly agree Agree Ambivalent Disagree Strongly disagree

3. **Taking part was not too onerous**

Strongly agree Agree Ambivalent Disagree Strongly disagree

4. **There were too many tasks**

Strongly agree Agree Ambivalent Disagree Strongly disagree

5. **There were too many blood samples**

Strongly agree Agree Ambivalent Disagree Strongly disagree

6. **There were too many questionnaires**

Strongly agree Agree Ambivalent Disagree Strongly disagree

7. **Taking part inconvenienced me**

Strongly agree Agree Ambivalent Disagree Strongly disagree

Please explain……

8. **I had side effects from taking part**

Strongly agree Agree Ambivalent Disagree Strongly disagree

9. **I think I know whether I had melatonin or placebo first**

Yes No (please state…….)

10. **I would take melatonin during night shifts if it was available**

Strongly agree Agree Ambivalent Disagree Strongly disagree

16.12 APPENDIX 12

Focus group discussion template

Introduction of researchers and give details of mutual respect and confidentiality code.
Reminder that the discussion would be recorded but that no names will be used in the analysis and reporting.

Organisation of the trial and communication with researchers.
Acceptability of the trial design, number of tasks, tests, questionnaires.
How did they feel about taking part?
Any barriers they came across?
Anything they could suggest to facilitate recruitment to a similar trial?
How did the drug(s) make them feel?
Did they have any side effects?
Could they tell if they had melatonin or placebo first?
Would they take melatonin if it was available?